REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 14, 40 and 58-64 are in the case.

I. CLAIM AMENDMENTS

Independent claim 14 has been amended to recite a pharmaceutical composition comprising at least one CD23-binding peptide consisting of the amino acid sequence Phe-His-Glu-Asn-Trp-Pro-Ser (SEQ ID NO:1), and a pharmaceutically acceptable carrier. Support appears in the originally filed specification, for example at page 16, lines 8-24, Examples 6 and 7.

Claim 59 has been amended to specify a CD23-binding peptide, wherein the peptide **consists of** the amino acid sequence of any one of SEQ ID NOs: 2 to 10, 31, 32, 34, 35, 40, 43 and 53-61. Support for these sequences is to be found in original claims 3, 5, 6 and in the sequence listing filed on November 1, 2006.

Support for CD23-binding activity for SEQ ID NOs: 31, 32, 34, 35, 40, 43 and 53-61 is to be found in Table 1 under references of compounds n° 333, 398, 299, 327, 331, 328, 436, 437, 490, 489, 491, 411, 492, 410 and 249. For ease of reference, a copy of Tables 1 and 2, as contained at pages 25-26 and 28 of the present application, is attached where each sequence is indicated.

Claims 61-63 have been amended to clarify the wording.

With the above-discussed amendments, it is believed that the formal points raised on page 3 of the Action with regard to claims 14 and 61-63 have been obviated.

Withdrawal of those points, including the 35 U.S.C. §112, second paragraph rejection of claims 14 and 61-63, are respectfully requested.

No new matter is entered. In addition, all amendments have been effected without prejudice to the possibility of filing a continuing application directed to any subject matter disclosed in the present application.

II. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 14, 40 and 58-64 are rejected under 35 U.S.C. §112, first paragraph, for the reasons stated on pages 4-11 of the Action. It is believed this rejection has been obviated by the present amendments. Thus, the claims as amended relate to CD23-binding peptides which have been synthesized and tested by the inventors, consisting of the amino acid sequences of SEQ ID NO: 1-10, 31, 32, 34, 35, 40, 43 and 53-61.

Claim 14 has been limited to the peptide of SEQ ID NO: 1, as suggested in the Action. Claim 59 has been limited to peptides specifically listed in Tables 1 and 2. In this regard, the Action asserts (paragraph 18, page 5) that "*only the specific peptides of SEQ ID NO: 1-7 inhibit iNOS production as shown in Table 2*". This assertion is respectfully traversed. Table 2 of the present application is attached, where each sequence is identified.

With the amendments and arguments presented above, it is believed the outstanding formal rejection should be withdrawn. Such action is respectfully requested.

III. THE ANTICIPATION REJECTION

Claims 14, 40 and 59 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Jouault *et al.* (Jouault), DE19749277, JP2002187899 or Santamaria *et al.* (Santamaria). The rejections are respectfully traversed.

As noted earlier, claim 14 has been limited to the peptide "consisting of" SEQ ID NO: 1 and claim 59 has been limited to peptides "consisting of" SEQ ID NO: 2-10, 31, 32, 34, 35, 40, 43 and 53-61. The rejections over Jouault, JP2002187899 and Santamaria have thus been overcome.

DE19749277 relates to chromatographic reagents useful for separation of albumin from biological fluids by affinity chromatography. The FHENWPS peptide is attached to a carrier material such as agarose. The only reference to PBS (column 2, lines 24-33) is for washing the agarose. Thus, DE19749277 does not disclose a pharmaceutical composition or a pharmaceutically acceptable carrier. Therefore, the anticipation rejection over DE19749277 is moot.

Furthermore, the rejection of paragraph 22, relative to SEQ ID NOS: 32 and 43, has been overcome, since the amino acids "Xaa" of SEQ ID NOS: 32 and 43 have been respectively limited to "N methyl glycin" and "beta alanine", according to sequences present in Table 1. The term "beta A" corresponds to beta alanine and the term "Sar" to N-methyl glycine, as defined page 24 of the present application. Withdrawal of the anticipation rejection over DE19749277 is respectfully requested.

IV. THE OBVIOUSNESS REJECTION

Claims 14 and 59-63 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Jouault, or DE19749277, or Santamaria, or JP2002187899 in view of US Patent No. 5,028,592, or Heck *et al.*, or Harlow *et al.* The rejections are respectfully traversed.

None of cited documents describes or suggests the pharmacological activity or the CD23-binding activity of the FHENWPS peptide. None of cited documents discloses or suggests CD23-binding peptides of SEQ ID NO: 2-10, 31, 32, 34, 35, 40, 43 and 53-61. Based on this, the skilled person, as of the filing date of the present application, would have not have envisaged the binding affinities of the peptides described for CD23 molecule, nor the pharmacological activity of the FHENWPS peptide, based on the cited references, taken singly or in combination.

It is clear, therefore, that the claimed peptides of SEQ ID NO: 2-10, 31, 32, 34, 35, 40, 43 and 53-61 and a pharmaceutical composition comprising the peptide of SEQ ID NO: 1, are not anticipated by, or rendered unpatentable in view of, the cited combination of references. Withdrawal of the obviousness rejections is respectfully requested.

US 5,028,592, Heck et *al.* and Harlow et *al.* have been cited to support the notion that modifying a peptide by adding acyl, acetyl or amidated groups (US 5,028,592), using D-isomers of amino acids (Heck *et al.*) or labelling a peptide (Harlow *et al.*) is an obvious approach. This is not correct.

The relevant inquiry is would the skilled person, as of the filing date of the present application, have had a reasonable expectation that the peptide of SEQ ID NO:

1 would bind CD23 and have utility in treating rheumatoid arthritis. None of the above-mentioned documents describes a peptide binding CD23 nor a peptide having activity on inhibition of iNOS production.

The Action states in item 27 that "*the intrinsically property of the claimed peptide such as CD23-binding activity as now claimed must be present*". This is not correct. In order to demonstrate the CD23-binding activity as well as NO-inhibiting activity, the present inventors had to develop suitable protocols carried out in specific experimental conditions described in experimental part of the application. This would not have been obvious to the skilled person as of the filing date of the present case. Withdrawal of all the rejections and allowance of the application are, accordingly, respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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Attachment: Tables 1 and 2

Table 1

	Position									
Compound	1	2	3	4	5	6	7	8	Comment	Activity
243	Ac	H	E	N	W	P	S	CONH2		+++
244		H	E	N	W	P	S	CONH2		+++
222		H	E	N	Tic	P	S			++
300		H	E	N	4 Indolyl A	P	S			++
288		H	N	E	W	P	S			++
SEQ 61 249		H	E	N	W	P	$CONH_2$			+++
289		H	E	P	W	R	S			++
283		H	E	N	beta W	P	S			++
281		H	P	N	W	R	S			+++
250		s	p	w	n	c	h	$CONH_2$		+++
290		H	Cys	N	W	Cys	S			++
306		H	E*	N	W	K	S		cyclic E2K	+++
SEQ 31 333		H	E	N	W	K	S			+++
274		H	E	N	W	cyclo L	S		cyclic H2T	++
298		H	E	N	W	P	S	G	cyclic H2T	++
SEQ 34 299		H	E	N	W	G	S		cyclic H2T	++
SEQ 35 327		H	E	N	W	E	S		cyclic H2E	+++
353	F	H	E	N	W	E	S		cyclic H2E	++
349	F	H	E	N	W	P	A			+++
316	F	H	E	N	W	A	S			+++
329	F	H	E	N	A	P	S			+++
SEQ 40 331	F	H	E	A	W	P	S			++
337	F	H	A	N	W	P	S			++
338	F	A	E	N	W	P	S			++
SEQ 43 328	F	H	E	N	W	beta A	S			+++
330	F	H	E	N	beta A	P	S			++
332	F	H	E	beta A	W	P	S			++
340	F	H	beta A	N	W	P	S			+++
339	F	beta A	E	N	W	P	S			+++
368/369	F	h	E	N	W	P	S			+++
367	F	H	E	n	W	P	S			++
366	F	H	E	N	w	P	S			+++
334	F	H	E	N	W	p	S			++
359	F	H	E	N	Tpi	P	S			++
364		H	E	Q	W	P	S			++
384		R	E	N	W	P	S			+++
392		H	E	N	W	Beta A	S		cyclic H2T	++
SEQ 32 398		H	E	N	W	Sar	S		cyclic H2T	++
377	CGG	F	H	E	N	W	P	S	Fluor	++
400		H	Q	N	W	P	S	$CONH_2$		++
405		H	E	Q	W	cyclo L	S			++
397	S	P	W	N	E	H	P		scrambled	++
420 A		H	E	N	W	cCpma	S		cyclic H2T	+++

SEQ 58	411			Ac	N	W	CO_2H			+++
	409			Ac	N	W	G	CO_2H		+++
SEQ 60	410			Ac	N	W	Beta A	CO_2H		+++
	435A		H	C	N	W	C	E	cyclic H2T & disulfide (1st diastereomer)	+++
	435B		H	C	N	W	C	E	cyclic H2T & disulfide (2nd diastereomer)	+++
SEQ 53	436		H	E	N	A	P	S	same as 329	+++
SEQ 54	437		H	E	N	W	S		cyclic H2T	+++
	440		H	E	N	W	Orn	S	cyclic Orn2T	+++
SEQ 56	489		NH_2	G[allyl-]	N	W	G[allyl-]		cyclic: allyl-sidechain metathesis	+++
SEQ 55	490			G[allyl-]	N	W	G[allyl-]	S	bicyclic: allyl-sidechain metathesis & cyclic H2T	+++
SEQ 57	491			Ac	w	n	CO_2H		D amino retro inverso	++++
SEQ 59	492			Ac	n	w	CO_2H		D amino inverso	++

Example 4- Cell cultures

Monocytes are isolated from normal human peripheral blood. Samples are collected from normal volunteers (20-50 years) by blood bank. They are all tested for the absence of HIV or HBV contaminations prior to use. Human normal mononuclear cells are obtained by Ficoll (Histopaque, Sigma) gradient separation of peripheral blood leukocytes. Monocytes are separated from lymphocytes by adherence to plastic dishes coated with fetal calf serum (FCS) as described (Vouldoukis I., *et al.*, Proc. Natl. Acad. Sci. USA., 92 : 7804-7808 1995). Following this procedure, >90% of cells express CD14 antigen and display cytochemical characteristics of monocytes. The cells are then incubated in DMEM supplemented with L-non-essential amino acids, sodium pyruvate, glutamine, penicillin, streptomycin, and 10% FCS (all from Gibco Laboratories, Grand Island, NY). Above culture medium, chemicals, and FCS are tested for the absence of direct activation effect on human monocytes (CD23 expression and TNF-α production as activation markers). Following 24-48 hr adherence to culture flasks, these cells differentiate into macrophage-like cells displaying non-specific esterase activity that is inhibited by sodium fluoride.

Normal human donor-derived adherent cells have low if any surface CD23 expression and are designated in the present work as macrophages. CD23 expression is

fetal calf serum (FCS) (all from Gibco Laboratories, Grand Island, NY)

CD23-MoAb (clone 25) (Immunotech, Marseille Lumigny, France).

Following quantitation of nitrites, a percentage inhibition relative to controls is calculated. The following results demonstrating inhibition of iNOS production were obtained:

Table 2

	Name	Sequence	% Inhibition
SEQ 57	491	Ac w n CO_2H	94
SEQ 58	411	Ac N W CO_2H	84
SEQ 55	490	G[allyl-] N W G[allyl-] S	81
SEQ 4	P30L	F H E N W P	78
SEQ 59	492	Ac n w CO_2H	77
SEQ 5	P30M	F H E N W P T	76
SEQ 1	p30A	F H E N W P S	74
SEQ 32	398	H E N W Sar S	74
SEQ 34	299	H E N W G S	74
SEQ 7	P30K	H E N W P S	74
SEQ 6	P30O	F H E Q W P S	73
SEQ 31	333	H E N W K S	69
SEQ 2	p30D	F H E F W P T	68
SEQ 3	p30E	F H S Q W P N	65
SEQ 56	489	NH_2 G[allyl-] N W G[allyl-]	62
SEQ 60	410	Ac N W BetaA CO_2H	61
SEQ 53	436	H E N A P S	60
SEQ 35	327	H E N W E S	60
SEQ 54	437	H E N W S	56
SEQ 10	P30G	F H K P W R A	55
SEQ 40	331	F H E A W P S	43
SEQ 43	328	F H E N W betaA S	26

Example 7- Analysis of CD23-specific binding.